AMENDMENTS TO THE SPECIFICATION:

Pursuant to 37 C.F.R. § 1.121, please amend the specification as follows:

On the title page, please replace the title "Novel Co-Stimulatory Molecules" with the following title: --Co-Stimulatory Polypeptides--.

On page 1, line 5, please replace the title "Novel Co-Stimulatory Molecules" with the following title: --Co-Stimulatory Polypeptides--.

Please replace the paragraph beginning at page 5, line 18 with the following amended paragraph:

In one aspect, the invention provides an isolated or recombinant polypeptide comprising an extracellular domain sequence, said extracellular domain sequence having at least about 75% amino acid sequence identity to an extracellular domain sequence of, or the full-length sequence of, at least one of SEQ ID NOS:48-68, 174-221, 283-285, and 290-293, and is not a naturally-occurring extracellular domain sequence, and wherein said polypeptide has a CD28/CTLA-4 binding affinity ratio equal to or greater than the CD28/CTLA-4 binding affinity ratio of human B7-1. Some such polypeptides induce T-cell proliferation or T-cell activation or both T-cell proliferation and T-cell activation. In some embodiments, the T cell activation or proliferation response is at least equal to or greater than that caused ~~cause~~ by WT hB7-1. Other such polypeptides modulate T-cell activation, but do not induce proliferation of purified T-cells activated by soluble anti-CD3 mAbs.

Please replace the paragraph beginning at page 7, line 13 with the following amended paragraph:

The invention further provides isolated or recombinant polypeptides comprising a sequence having at least about 95% identity to at least one of SEQ ID NOS:69-92, 222-252, 286-289, or a subsequence thereof comprising the extracellular domain, wherein said sequence (a) is a non naturally-occurring sequence, and (b) comprises at least one of: Gly at position 2; Thr at position 4; Arg at position 5; Gly at position 8; Pro at position 12; Met at position 25; Cys at position 27; Pro at position 29; Leu at position 31; Arg at position 40; Leu at position 52; His at position 65;

Ser at position 78; Asp at position 80; Tyr at position 87; Lys at position 120; Asp at position 122; Lys at position 129; Met at position 135; Phe at position 150; Ile at position 160; Ala at position 164; His at position 172; Phe at position 174; Leu at position 176; Asn at position 178; Asn at position 186; Glu at position 194; Gly at position 196; Thr at position 199; Ala at position 210; His at position 212; Arg at position 219; Pro at position 234; Asn at position 241; Leu at position 244; Thr at position 250; Ala at position 254; Tyr at position 265; Arg at position 266; Glu at position 273; Lys at position 275; Ser at position 276; an amino acid deletion at position 276; or Thr at position 279, wherein the position number corresponds to that of the human B7-1 amino acid sequence (SEQ ID NO:278), wherein said polypeptide has a CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio equal to or greater than the CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio of human B7-1.

Please replace the paragraph beginning at page 8, line 1 with the following amended paragraph:

In another aspect, the invention provides isolated or recombinant polypeptides comprising a sequence that differs from a primate B7-1 sequence in at least one mutation selected from: Ser 12 Pro; Leu 25 Met; Gly 27 Cys; Ser 29 Pro; Lys 40 Arg; His 52 Leu; Tyr 65 His; Glu 122 Asp; Glu 129 Lys; Thr 135 Met; Thr 164 Ala; Ser 174 Phe; Glu 196 Gly; Ala 199 Thr; Thr 210 Ala; Lys 219 Arg; Thr 234 Pro; Asp 241 Asn; Val 254 Ala; Arg 275 Lys; Arg 276 Ser; or Arg 279 Thr; the mutation being indicated relative to human B7-1 with the amino acid sequence shown in SEQ ID NO:278, wherein said sequence does not occur in nature, and wherein said polypeptide has a CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio equal to or greater than the CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio of human B7-1.

Please replace the paragraph beginning at page 8, line 11 with the following amended paragraph:

Also included are isolated or recombinant polypeptides comprising a sequence having at least about 75% identity to at least one of SEQ ID NOS:263-272, or a subsequence thereof comprising the extracellular domain, where the sequence is not naturally-occurring, and the polypeptide has a CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio equal to or greater than the CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio of human B7-1.

Please replace the paragraph beginning at page 10, line 28 with the following amended paragraph:

Gly at position 2; Thr at position 4; Arg at position 5; Gly at position 8; Pro at position 12; Met at position 25; Cys at position 27; Pro at position 29; Leu at position 31; Arg at position 40; Leu at position 52; His at position 65; Ser at position 78; Asp at position 80; Tyr at position 87; Lys at position 120; Asp at position 122; Lys at position 129; Met at position 135; Phe at position 150; Ile at position 160; Ala at position 164; His at position 172; Phe at position 174; Leu at position 176; Asn at position 178; Asn at position 186; Glu at position 194; Gly at position 196; Thr at position 199; Ala at position 210; His at position 212; Arg at position 219; Pro at position 234; Asn at position 241; Leu at position 244; Thr at position 250; Ala at position 254; Tyr at position 265; Arg at position 266; Glu at position 273; Lys at position 275; Ser at position 276; an amino acid deletion at position 276; and Thr at position 279, wherein the position number corresponds to that of the human B7-1 amino acid sequence (SEQ ID NO:278), and wherein said polypeptide has a CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio equal to or greater than the CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio of human B7-1.

Please replace the paragraph beginning at page 21, line 27 with the following amended paragraph:

Figure 1A is a schematic representation of exemplary interactions between 1) a T cell receptor (TCR) and antigenic peptide presented in the groove of a major histocompatibility complex (MHC) molecule, and 2) a recombinant CD28BP polypeptide of the invention expressed on the surface of an antigen-presenting cell (APC) and a CD28 receptor on a T cell. Figure 1B is a schematic representation of exemplary interactions between 1) a TCR and antigenic peptide presented in the groove of a MHC molecule, and 2) a recombinant CTLA-4BP ~~CTL4-BP~~ polypeptide of the invention expressed on the surface of an APC and a CTLA-4 receptor on a T cell. The representation illustrates the principle by which recombinant polypeptides of the invention which preferentially bind the CD28 or CTLA-4 receptor effectuating enhanced or suppressed T cell activation.

Please replace the paragraph beginning at page 23, line 7 with the following amended paragraph:

Figure 6A is a schematic representation of an exemplary competitive FACS binding profile for a CTLA-4BP clone for soluble CD28-Ig receptor and soluble CTLA-4-Ig receptor. Figure 6B is a schematic representation of an exemplary competitive FACS binding profile for a CD28BP ~~CD284BP~~ clone for soluble CD28-Ig receptor and soluble CTLA-4-Ig receptor.

Please replace the paragraph beginning at page 23, line 7 with the following amended paragraph:

Figures 8A-8B present schematic representations of the amino acid sequences of CD28BP-15 ~~CD28BP-12~~ and CTLA-4BP 5x4-12c and the genealogy of these sequences.

Please replace the paragraph beginning at page 38, line 29 with the following amended paragraph:

A ~~An~~ "binding affinity ratio" refers to a relative ratio of the binding affinity of a molecule of interest (e.g., a recombinant ligand, such as a NSCM polypeptide) for a first molecule (e.g., a first receptor, such as CD28 receptor) to the binding affinity of the same molecule of interest to a second molecule (e.g., a second receptor, such as CTLA-4 receptor). In one aspect, the relative binding affinity ratio may be determined by visual inspection, such as by, e.g., examining a FACS binding profile that displays the binding affinity profile of the molecule of interest to both receptors, and evaluating the degree of relative binding of the molecule of interest to each of the first and second receptors. The results of this determination can be compared with a similar examination and evaluation of a FACS binding affinity profile displaying the binding affinity of a control molecule (e.g., wild-type ligand, such as a WT human, primate, or mammalian B7-1) to both receptors, wherein the degree of relative binding of the control molecule to each of the receptors is evaluated. These and other procedures described below can be used to determine a CD28/CTLA-4 binding affinity ratio for a CD28BP polypeptide of the present invention and a CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio for a CTLA-4BP polypeptide of the present invention. Alternatively, a binding affinity ratio can be determined by making a ratio between a quantitative measurement of the binding affinity of the molecule of interest (e.g., ligand) for the first receptor and a quantitative measurement of the binding affinity of the molecule of interest for the second receptor

using known procedures for measuring binding affinities. For example, known methods for measuring the binding affinity of human (or other mammalian) B7-1 for each of CD28 and CTLA-4 receptors can be used.

Please replace the paragraph beginning at page 46, line 18 with the following amended paragraph:

The invention includes isolated or recombinant nucleic acids that each comprise a polynucleotide sequence selected from: (a) a polynucleotide sequence selected from SEQ ID NOS:22-45, 143-173, or a complementary polynucleotide sequence thereof; (b) a polynucleotide sequence encoding a polypeptide selected from SEQ ID NOS:69-92, 222-247, 286-289, or a complementary polynucleotide sequence thereof; (c) a polynucleotide sequence which hybridizes under highly stringent conditions over substantially the entire length of polynucleotide sequence (a) or (b); and (d) a polynucleotide sequence comprising all or a fragment of (a), (b), or (c); wherein (c) or (d) encodes a polypeptide having a non naturally-occurring sequence comprising at least one of: Gly at position 2; Thr at position 4; Arg at position 5; Gly at position 8; Pro at position 12; Met at position 25; Cys at position 27; Pro at position 29; Leu at position 31; Arg at position 40; Leu at position 52; His at position 65; Ser at position 78; Asp at position 80; Tyr at position 87; Lys at position 120; Asp at position 122; Lys at position 129; Met at position 135; Phe at position 150; Ile at position 160; Ala at position 164; His at position 172; Phe at position 174; Leu at position 176; Asn at position 178; Asn at position 186; Glu at position 194; Gly at position 196; Thr at position 199; Ala at position 210; His at position 212; Arg at position 219; Pro at position 234; Asn at position 241; Leu at position 244; Thr at position 250; Ala at position 254; Tyr at position 265; Arg at position 266; Glu at position 273; Lys at position 275; Ser at position 276; an amino acid deletion at position 276; and Thr at position 279, wherein the position number corresponds to that of the human B7-1 amino acid sequence (SEQ ID NO:278), and wherein said polypeptide has a CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio equal to or greater than the CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio of human B7-1.

Please replace the paragraph beginning at page 52, line 26 with the following amended paragraph:

In addition, essentially any nucleic acid can be custom ordered from any of a variety of commercial sources, such as The Midland Certified Reagent Company (mcrc@oligos.com), The Great American Gene Company (see genco website with the extension of ".com") ~~(http://www.genco.com)~~, ExpressGen Inc. (see expressgen website with the extension of ".com") ~~(www.expressgen.com)~~, Operon Technologies Inc. (Alameda, CA) and many others. Similarly, peptides and antibodies can be custom ordered from any of a variety of sources, e.g., PeptidoGenic (see pkim@ccnet with the extension of ".com") ~~(pkim@ccnet.com)~~, HTI Bio-products, Inc. (see htbio website with the extension of ".com") ~~(http:// www.htibio.com)~~, BMA Biomedicals Ltd. (U.K.), Bio.Synthesis, Inc., and many others.

Please replace the paragraph beginning at page 59, line 27 with the following amended paragraph:

Promoters for use with NCSM polynucleotide sequences of the present invention include recombinant, mutated, or recursively recombined (e.g., shuffled) promoters, including optimized recombinant CMV promoters, as described in copending, commonly assigned US Patent Application Serial No. 09/886,942 ~~No. _____~~, entitled "Novel Chimeric Promoters," filed June 21, 2001 as LJAQ Attorney Docket No. 02-031910US, incorporated herein by reference in its entirety for all purposes. Such promoters can be employed in expression vectors comprising nucleotide sequences encoding, e.g., NCSM polypeptides, soluble NSCM-ECD polypeptides, or NCSM-ECD-Ig fusion proteins, or WT hB7-1, or fragments of any of these.

Please replace the paragraph beginning at page 99, line 29 with the following amended paragraph:

Synthetic recombination methods can also be used, in which oligonucleotides corresponding to targets of interest are synthesized and reassembled in PCR or ligation reactions which include oligonucleotides which correspond to more than one parental nucleic acid, thereby generating new recombined nucleic acids. Oligonucleotides can be made by standard nucleotide addition methods, or can be made, e.g., by tri-nucleotide synthetic approaches. Details regarding such approaches are found in the references noted above, including, e.g., WO 00/42561 by Crameri et al., "Oligonucleotide ~~Olgonucleotide~~ Mediated Nucleic Acid Recombination;" PCT/US00/26708 by Welch et al., "Use of Codon-Varied Oligonucleotide Synthesis for Synthetic Shuffling;" WO

00/42560 by Selifonov et al., "Methods for Making Character Strings, Polynucleotides and Polypeptides Having Desired Characteristics;" and WO 00/42559 by Selifonov and Stemmer "Methods of Populating Data Structures for Use in Evolutionary Simulations."

Please replace the paragraph beginning at page 111, line 1 with the following amended paragraph:

In yet another embodiment, the invention provides isolated or recombinant polypeptides comprising a sequence according to the formula:

MGHTM-X6-W-X8-SLPPK-X14-PCL-X18-X19-X20-QLLVLT-X27-LFYFCSGITPKSVTKRVKETVMLSCDY-X55-TSTE-X60-LTSLRIYW-X69-KDSKMVLAILPGKVQVWPEYKNRTITDMNDN-X101-RIVI-X106-ALR-X110-SD-X113-GTYTCV-X120-QKP-X124-LKGAYKLEHL-X135-SVRLMIRADFPVP-X149-X150-X151-DLGNPSPNIRRLICS-X167-X168-X169-GFPRPHL-X177-WLENGEELNATNTT-X192-SQDP-X197-T-X199-LYMISSEL-X208-FNVTNN-X215-SI-X218-CLIKYGEL-X227-VSQIFPWSKPKQEPPIDQLPF-X249-VIIPVSGALVL-X261-A-X263-VLY-X267-X268-ACRH-X273-ARWKRTRRNEETVGTE RLSPIYLGSAQSSG (SEQ ID NO:284), or a subsequence thereof comprising the extracellular domain, wherein position X6 is Lys or Glu; position X8 is Arg or Gly; position X14 is Arg or Cys; position X18 is Trp or Arg; position X19 is Pro or Leu; position X20 is Ser or Pro; position X27 is Asp or Gly; position X55 is Asn or Ser; position X60 is Glu or Lys; position X69 is Gln or Arg; position X101 is Pro or Leu; position X106 is Leu or Gln; position X110 is Pro or Leu; position X113 is Lys or Ser; position X120 is Val or Ile; position X124 is Val or Asp; position X135 is Thr or Ala; position X149 is Thr, Ser, or del; position X150 is Ile or del; position X151 is Asn or Thr; position X167 is Thr or del; position X169 is Ser or del; position X169 is Gly or del; position X177 is Cys or Tyr; position X192 is Val or Leu; position X197 is Gly or Glu; position X199 is Glu or Lys; position X208 is Gly or Asp; position X215 is His or Arg; position X218 is Ala or Val; position X227 is Ser or Leu; position X249 is Trp, Leu, or Arg; position X261 is Ala or Thr; position X263 is Val, Ala, or Ile; position X267 is Arg or Cys; position X268 is Pro or Leu; and position X273 is Gly or Val. Some such polypeptides have one or more of the properties of CD28 polypeptides described herein, including an ability to enhance an immune response, induce a T cell activation or proliferation response, exhibit a CD28/CTLA-4 ~~CD28BP/CTLSA-4~~ binding affinity ratio equal to or greater than that of hB7-1, and/or alter cytokine production. For some such

polypeptides, the induced T cell response is equal to or greater than that of hB7-1. In one embodiment, some such polypeptides comprise an extracellular domain sequence of any one of SEQ ID NOS:51-56, 58, 61, 66, 67, 174-179, 181, 185-187, 189, 192-194, 197, 199, 202, 205, 208, 215, 217, 220, and 285.

Please replace the paragraph beginning at page 112, line 25 with the following amended paragraph:

The invention also provides isolated or recombinant polypeptides comprising a sequence according to the formula:

MGHTMKWGSLPPKRPCLWLSQLLVLTGLFYFCSGITPK SVTKRVKETVM-X50-SCDY-X55-X56-STEELTSLRIYWQKDSKMVL AILPGKVQVWPEYKNRTITD MNDNPRIVILALRLSD-X113-GTYTCV-X120-QK-X123-X124-X125-X126-G-X128-X129-X130-X131-EHL-X135-SV-X138-L-X140-IRADFPVPSITDIGHPAPNVK RIRCSASG-X170-FPEPRLAWMEDGEEL NAVNTTV-X193-X194-X195-LDTELYSVSSELD-X209-N-X211-TNNHSIVCLIKYGELSVSQIFPWSKPK QEPPIDQLPFWVI-X252-X253-VSGALVLTAVVLYCLACRHVAR (SEQ ID NO:290), or subsequence thereof comprising the extracellular domain, wherein position X50 is Leu or Pro; position X55 is Asn or Ser; position X56 is Ala or Thr; position X113 is Ser or Lys; position X120 is Ile or Val; position X123 is Pro or deleted; position X124 is Val, Asn, or Asp; position X125 is Leu or Glu; position X126 is Lys or Asn; position X128 is Ala or Ser; position X129 is Tyr or Phe; position X130 is Lys or Arg; position X131 is Leu or Arg; position X135 is Ala or Thr; position X138 is Arg or Thr; position X140 is Met or Ser; position X170 is Asp or Gly; position X193 is Asp or is deleted; position X194 is Gln or is deleted; position X195 is Asp or is deleted; position X211 is Val or Ala; position X252 is Ile or Val; and position X253 is Leu or Pro. Some such polypeptides have at least one of the properties of CD28 polypeptides described herein, including an ability to enhance an immune response, induce T cell activation or proliferation, exhibit a CD28/CTLA-4 ~~CD28BP/CTLSA-4~~ binding affinity ratio equal to or greater than that of hB7-1, and/or alter cytokine production. For some such polypeptides, the induced T cell response is equal to or greater than that of hB7-1.

Please replace the paragraph beginning at page 113, line 28 with the following amended paragraph:

In another aspect, the invention provides isolated or recombinant polypeptides comprising a sequence according to the formula:

MGHTMKWG-X9-LPPKRPCLWLSQLLVLTGLFYFCSG-X35-TPKSVTKRV KETVMLSCDY-X55-TSTEELTSLRIYWQKDSKMVLAILPGKVQVW PEYKNRTITDMNDNPRIVILALR-X110-SDSGTYTCVIQKP-X124-LKGAYKLEHL-X135-SVRLMIRADFPVPTINDLGNPSPNIRRLICSTSGGFPRPHLYWLENG-X183-ELNATNTT-X192-SQDPETKLYMISSELDFN-X211-TSN-X215-X216-X217-LCLVKYGDLTVSQ-X231-FYWQESKPTPSANQHLTWTIIIPVSAFGISVIIAVI LTCLTCRNAAIRRQRRENEV-X288-M-X290-SCSQSP (SEQ ID NO:292), or a subsequence thereof comprising the extracellular domain, wherein position X9 is Thr or Ser; position X35 is Ile or Thr; position X55 is Asn or Ser; position X110 is Leu or Pro; position X124 is Asp or Val; position X135 is Thr or Ala; position X183 is Lys or Glu; position X192 is Leu or Val; position X211 is Met or Thr; position X215 is His or is deleted; position X216 is Ser or is deleted; position X217 is Phe or is deleted; position X231 is Thr or Ser; position X288 is Lys or Glu; position X290 is Glu or Gln, and wherein said sequence is a non naturally-occurring sequence. Further, some such polypeptides have at least one of the properties of CD28 polypeptides described herein, including an ability to enhance an immune response, induce T cell activation or proliferation, exhibit a CD28/CTLA-4 ~~CD28BP/CTLSA-4~~ binding affinity ratio equal to or greater than that of hB7-1, and/or alter cytokine production. For some such polypeptides, the induced T cell response is equal to or greater than that of hB7-1.

Please replace the paragraph beginning at page 114, line 18 with the following amended paragraph:

In a preferred embodiment, some such polypeptides comprise two, three, four, five, six, eight, ten, or more of the following amino acids: Thr at position X9; Ile at position X35; Asn at position X55; Leu at position X110; Asp at position X124; Thr at position X135; Lys at position X183; Leu at position X192; Met at position X211; His at position X215; Ser at position X216; Phe at position X217; Thr at position X231; Lys at position X288; and Glu at position X290. In yet another preferred embodiment, some such polypeptides comprise a sequence of any one of SEQ ID NOS:48, 182, 183, 212, 214, 216, 218, 221, and 293.

Please replace the paragraph beginning at page 114, line 27 with the following amended paragraph:

In one aspect, the invention provides isolated or recombinant CTLA-4BP polypeptides each comprising a sequence having at least about 85%, 88%, 89%, 90%, 91%, 92&, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5% or more percent identity to at least one of SEQ ID NOS:69-92, 222-252, 286-289, or a subsequence thereof comprising the extracellular domain, wherein said sequence (a) is a non naturally-occurring sequence, and (b) comprises at least one of: Gly at position 2; Thr at position 4; Arg at position 5; Gly at position 8; Pro at position 12; Met at position 25; Cys at position 27; Pro at position 29; Leu at position 31; Arg at position 40; Leu at position 52; His at position 65; Ser at position 78; Asp at position 80; Tyr at position 87; Lys at position 120; Asp at position 122; Lys at position 129; Met at position 135; Phe at position 150; Ile at position 160; Ala at position 164; His at position 172; Phe at position 174; Leu at position 176; Asn at position 178; Asn at position 186; Glu at position 194; Gly at position 196; Thr at position 199; Ala at position 210; His at position 212; Arg at position 219; Pro at position 234; Asn at position 241; Leu at position 244; Thr at position 250; Ala at position 254; Tyr at position 265; Arg at position 266; Glu at position 273; Lys at position 275; Ser at position 276; an amino acid deletion at position 276; or Thr at position 279, wherein the position number corresponds to that of hB7-1 amino acid sequence (SEQ ID NO:278), wherein said polypeptide has a CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio equal to or greater than a CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio of hB7-1.

Please replace the paragraph beginning at page 116, line 30 with the following amended paragraph:

The invention also provides isolated or recombinant polypeptides each comprising a sequence that differs from a primate B7-1 sequence in at least one mutation selected from: Ser 12 Pro; Leu 25 Met; Gly 27 Cys; Ser 29 Pro; Lys 40 Arg; His 52 Leu; Tyr 65 His; Glu 122 Asp; Glu 129 Lys; Thr 135 Met; Thr 164 Ala; Ser 174 Phe; Glu 196 Gly; Ala 199 Thr; Thr 210 Ala; Lys 219 Arg; Thr 234 Pro; Asp 241 Asn; Val 254 Ala; Arg 275 Lys; Arg 276 Ser; or Arg 279 Thr. The mutation being indicated is relative to human B7-1 with the amino acid sequence shown in SEQ ID NO:278, the sequence does not occur in nature, and the polypeptide has a CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio equal to or greater than the CTLA-4/CD28 ~~CTLA-4/CD28BP~~

binding affinity ratio of human B7-1. The sequence of some such polypeptides differs from primate B7-1 sequence in at least two of said mutations. In some aspects, the primate B7-1 is hB7-1 (SEQ ID NO:278), and in some aspects, the sequence differs from the hB7-1 sequence in at least two mutations.

Please replace the paragraph beginning at page 117, line 11 with the following amended paragraph:

In another aspect, the invention provides isolated or recombinant CTLA-4BP polypeptides comprising a sequence having at least about 75%, 80%, 85%, 90%, 95%, or more percent identity to at least one of SEQ ID NOS:263-272, or a subsequence thereof comprising the ECD, wherein the sequence is not a naturally-occurring sequence, and the polypeptide has a CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio equal to or greater than the CTLA-4/CD28 ~~CTLA-4/CD28BP~~ binding affinity ratio of hB7-1.

Please replace the paragraph beginning at page 119, line 5 with the following amended paragraph:

In addition, the invention provides novel isolated or recombinant polypeptides corresponding to baboon and orangutan ~~organutan~~ B7-1. Such polypeptides comprise the sequence SEQ ID NO:93 or SEQ ID NO:94, or a subsequence thereof, wherein the subsequence comprises at least one of: the signal sequence, extracellular domain, transmembrane domain, and the cytoplasmic domain of the polypeptide.

Please replace the paragraph beginning at page 120, line 16 with the following amended paragraph:

The present invention also includes at least one NCSM polypeptide consensus sequence derived from a comparison of two or more NCSM polypeptide sequences described herein. For example, the present invention includes at least one CD28BP or CTLA-4BP polypeptide consensus sequences derived from a comparison of, respectively, two or more CD28BP or CTLA-4BP polypeptide sequences described herein. A CD28BP polypeptide consensus sequence as used herein refers to a nonnaturally-occurring or recombinant polypeptide that predominantly includes those amino acid residues that are common to all CD28BP polypeptides of the present invention

described herein (e.g., full-length and ECD polypeptides and fragments having activities described herein) and that includes, at one or more of those positions wherein there is no amino acid common to all subtypes, an amino acid that predominantly occurs at that position and in no event includes any amino acid residue that is not extant in that position in at least one CD28BP of the invention. A CD28BP polypeptide consensus sequence may have at least one property of a CD28BP polypeptide as described herein (e.g., CD28/CTLA-4 ~~CD28BP/CTLA-4BP~~ binding affinity ratio at least equal to greater than that of hB7-1; ability to enhance an immune response, stimulate T cell proliferation or activation).

Please replace the paragraph beginning at page 121, line 1 with the following amended paragraph:

A CTLA-4BP polypeptide consensus sequence refers to a nonnaturally-occurring or recombinant polypeptide that predominantly includes those amino acid residues which are common to all CTLA-4BP polypeptides of the present invention (e.g., full-length and ECD polypeptides) and that includes, at one or more of those positions wherein there is no amino acid common to all subtypes, an amino acid that predominantly occurs at that position and in no event includes any amino acid residue that is not extant in that position in at least one CTLA-4BP of the invention. A CTLA-4BP polypeptide consensus may have at least one property of a CTLA-4BP polypeptide as described herein (e.g., CTLA-4/CD28 ~~CTLA-4BP/CD28BP~~ binding affinity ratio at least equal to greater than that of hB7-1; suppress an immune response, or inhibit T cell proliferation or activation).

Please replace the paragraph beginning at page 121, line 24 with the following amended paragraph:

In one aspect, the invention provides the CD28BP consensus polypeptide sequence (SEQ ID NO:283) and the CTLA-4BP consensus polypeptide sequence (SEQ ID NO:286) and respective fragments or subsequences thereof that have at least one property of a CD28BP or CTLA-4BP polypeptide as described herein. A subsequence of a CD28BP or CTLA-4BP ~~CTLA-4~~ consensus sequence includes a sequence that substantially corresponds (via visual inspection of alignment) to each of the ECD, transmembrane domain, cytoplasmic domain, signal peptide, or

mature region of any respective CD28BP or CTLA-4BP polypeptide shown in the alignment in Figures 2A-2H and 3A-3H.

Please replace the paragraph beginning at page 132, line 21 with the following amended paragraph:

As a final determination of specificity, the pooled antisera is optionally fully immunoabsorbed with the *immunogenic* polypeptide(s) (rather than any control polypeptides) until little or no binding of the resulting immunogenic polypeptide subtracted pooled antisera to the immunogenic polypeptide(s) used in the immunoabsorption ~~immunoabsorbtion~~ is detectable. This fully immunoabsorbed ~~immunosorbed~~ antisera is then tested for reactivity with the test polypeptide. If little or no reactivity is observed (i.e., no more than 2x the signal to noise ratio observed for binding of the fully immunoabsorbed ~~immunosorbed~~ antisera to the immunogenic polypeptide), then the test polypeptide is specifically bound by the antisera elicited by the immunogenic protein.

Please replace the paragraph beginning at page 162, line 1 with the following amended paragraph:

In one aspect, the invention provides methods for modulating or altering a T-cell response specific to an antigen in a subject. Some such methods comprise administering ~~compris eadministering~~ to the subject at least one polynucleotide sequence comprising a NCSM polynucleotide described here (e.g., SEQ ID NOS:1-47,95-173, and 253-262) or at least one polynucleotide ~~polnucleotide~~ encoding a polypeptide comprising any of SEQ ID NOS:48-94, 174-252, 263-272 and 283-293 or fragment thereof, and a polynucleotide sequence encoding the antigen or antigenic fragment thereof. Each of the at least one polynucleotide sequences is expressed in the subject in an amount effective to modulate or alter a T cell response. In some such methods, the polypeptide or fragment thereof interacts with or binds a T cell surface receptor. In some such methods, T-cell response is enhanced as measured by assays described herein, and in some such methods, the enhanced T cell response is sufficient to eliminate cells bearing the antigen or antigenic fragment thereof. In other methods, the T-cell response is suppressed or inhibited as measured by assays described herein.

Please replace the paragraph beginning at page 163, line 30 with the following amended paragraph:

The invention includes therapeutic methods for activating or enhancing a T-cell response in a subject, wherein the subject may have a tumor or from whom a tumor was surgically ~~surgicall y~~ removed. Such methods comprise administering to the subject a composition that comprises a polynucleotide sequence encodes a NCSM polypeptide and an excipient, wherein the NCSM polypeptide is expressed by tumor cells or tumor-related cells of the subject, and the T-cell response is activated or enhanced against the tumor. For some such methods, the polynucleotide sequence encodes a soluble NCSM polypeptide. The composition may comprise a vector comprising the polynucleotide sequence that encodes a NCSM polypeptide. Further a therapeutically effective amount of the composition sufficient to enhance a T-cell response against the tumor may be administered. Pharmaceutical composition comprising an expression vector comprising a polynucleotide sequence that encodes a NCSM polypeptide and a pharmaceutically acceptable excipient are also provided.

Please replace the paragraph beginning at page 173, line 6 with the following amended paragraph:

The invention includes methods of designing or identifying CD28 agonists that enhance or inhibit signaling through either CD28 or CTLA-4 molecules of T-cells, based on visual viewing and/or analysis of the three-dimensional structure (e.g., ~~e.g,~~ X-ray crystallography), an analysis of the residues involved in CD28 and/or CTLA-4 binding, and the positions and types of such residues of any of the polypeptides of the invention as found in SEQ ID NOS:48-94, 174-252, 263-272, 283-293, or fragments thereof.

Please replace the paragraph beginning at page 173, line 30 with the following amended paragraph:

The invention includes methods of designing or identifying CD28 agonists that enhance or inhibit signaling through either CD28 or CTLA-4 molecules of T-cells, based on visual viewing and/or analysis of the three-dimensional structure (e.g., ~~e.g,~~ X-ray crystallography), an analysis of the residues involved in CD28 and/or CTLA-4 binding, and the positions and types of

such residues of any of the polypeptides of the invention as found in SEQ ID NOS:48-94, 174-252, 263-272, 283-293, or fragments thereof.

Please replace the paragraph beginning at page 178, line 25 with the following amended paragraph:

The cell lines or activated PBMCs were harvested and mRNA or total RNA was isolated using FastTrack® ~~FastTrack~~ 2.0 mRNA Isolation Kit ~~isolation kit~~ (Invitrogen, Carlsbad, CA) or Promega RNAgents® ~~RNAgents~~ Total RNA Isolation System Kit ~~kit~~ (Promega, Madison, WI), respectively. Primers used to clone the respective mammalian B7-1 cDNAs were designed based on published sequences for human, bovine and rabbit B7-1 genes (see, e.g., Freeman, G.J. et al. (1989) J Immunol 143:2714-22; Parsons, K.R. & Howard, C.J. (1999) Immunogenetics 49:231-4; and Isono, T. & Seto, A. (1995) Immunogenetics 42:217-20)(see also, for human B7-1, GenBank Access. Nos. U33208, AF024703; Cow B7-1, GenBank Acc. No. Y09950; rabbit B7-1, GenBank Access. No. D49843. The primers, which were purchased from Gibco BRL, contained a Bam H I site 5' of the start codon and a Kpn I site 3' of the stop codons. cDNA was generated using the mRNA or total RNA in the Invitrogen cDNA Cycle® Kit ~~Cycle kit~~. The cDNAs were generated by RT-PCR, which was performed using the cDNA Cycle® Kit ~~Cycle kit~~ (Invitrogen, Carlsbad, CA) according to the manufacturer's instructions and standard techniques. Each cDNA was then used as a template for PCR generation of, e.g., double-stranded cDNA using primer(s) specific for each species.

Please replace the paragraph beginning at page 182, line 19 with the following amended paragraph:

Plasmid was recovered from the sorted cells by lysis with 400 µl Hirt's solution (0.6% sodium dodecyl sulfate (SDS), 10 milliMolar (mM) EDTA pH 8.0) for 0.5 hour, the addition of 100 µl of 0.5 M NaCl to the lysate, and the lysate incubated over night. The lysate was spun (e.g., ~~e.g.,~~ centrifuged at 14,000xg for 60 minutes), extracted with equal volume of Phenol/Chloroform, ethanol precipitated, and resuspended in 10 µl TE buffer. The isolated plasmid was used to transform *E. coli* strain DH10B and the transformed cells were plated on LB agar plates. All colonies were harvested and combined and plasmid DNA was isolated using the Qiagen Maxiprep kit.

Please replace the top header of Table 5 beginning on page 209, line 4 (header of Table 5) with the following:

Table 5

Clone ID	**Nucleotide Position**	**Amino Acid Position ~~Postion~~**	**3' end ECN**

Please replace the top header of Table 6 beginning on page 210, line 16 (top header of Table 6) with the following:

Table 6

Clone ID	**Nucleotide Position**	**Amino Acid Position ~~Postion~~**	**3' end ECN**

Please replace the bottom header of Table 6 beginning on page 210, line 16 (bottom header of Table 6) with the following:

Table 6

Clone ID	**Nucleotide Position**	**Amino Acid Position ~~Postion~~**	**5' end Fc**

Please replace the paragraph beginning at page 217, line 26 with the following amended paragraph:

A representative experiment using crosslinked fusion proteins and purified human T cells is shown in Figure 20A. Increasing concentrations (conc) of soluble Ig-fusion proteins of hB7.1 (solid square), CD28BP-15 (open triangle) and a control antibody ~~goat anti-human~~ human IgG Fc (open circle) were added to the cultures as indicated. A fixed concentration (125 ug/ml) of goat anti-human IgG Fc was preincubated with soluble Ig-fusion proteins prior to use. The data represent a mean+/- STD of C.P.M. The crosslinked CD28BP-15-ECD-Ig-fusion protein and WT hB7-1-ECD-Ig fusion protein induced a strong proliferative effect on purified human T cells cultured in the presence of anti-CD3 mAbs.

Please replace the text header beginning on page 219, line 29 with the following:

G. Variations of Soluble NCSM-ECD-Ig Fusion Proteins and Related Nucleic Acid ~~Acids~~ Sequences

Please replace the paragraph beginning at page 222, line 20 with the following amended paragraph:

In this example, the CMV Towne promoter was used for driving the expression of the transgene in mammalian cells. Alternatively, other CMV promoters or non-naturally occurring recombinant or chimeric CMV promoters can be used; for example, a chimeric or recombinant promoter, including an optimized CMV promoter, as described in copending, commonly assigned USSN 09/886,942, ~~_____~~, entitled "Novel Chimeric Promoters," filed June 21, 2001 as LJAQ Attorney Docket No. 02-031910US, can be used. Different strains of CMV can be obtained from ATCC. Strains AD169 (VR-538; Rowe, W. (1956) Proc. Soc. Exp. Biol. Med. 145:794-801) and Towne (VR-977; Plotkin, S.A. (1975) Infect. Immun. 12:521-27) were isolated from human patients with CMV infections, while strains 68-1 (Asher, D.M. (1969) Bacteriol. Proc. 269:91) and CSG (Black, H. (1963) Proc. Soc. Exp. Biol. Med. 112:601) were isolated from Rhesus and Vervet monkeys, respectively. Other viral promoters, e.g., from RSV and SV40 virus, and cellular promoters, such as the actin and SRα promoter, and the like, and other promoters known to those of skill in the art, confer ubiquitous transcription in mammalian cells as well. For cell type-specific transcription, the use of cell type-specific promoters, such as muscle specific, liver specific, keratinocyte specific, and the like, and others known to those of skill in the art can be used.

Please replace the paragraph beginning at page 224, line 11 with the following amended paragraph:

The nucleotide sequence encoding a NCSM polypeptide (e.g., a CD28BP or CTLA-4BP polypeptide or fragment thereof, such as an ECD domain) or any other immunomodulatory molecule can be isolated by PCR with BamHI and KpnI restriction enzyme recognition sequences in the PCR forward and reverse primer as described above. In this example, a polynucleotide sequence encoding a CD28BP polypeptide (e.g., ~~e.g.,~~ CD28BP-15 polypeptide (SEQ ID NO:19) is incorporated into the pMaxVax ~~pMAxVax~~ 10.1 vector. To verify the correct sequence of the PCR products, the fragments are cloned conveniently into the TOPO® cloning vectors (Invitrogen) for

sequencing according to the manufacturer's protocols. After BamHI and KpnI digestion and gel purification, the genes are cloned into a mammalian expression vector to confirm the expression of the gene. To clone the genes into the polylinker of pMaxVax, the vector pMaxVax 10.1mp (Fig. 21 with modified polylinker as described above) was digested with BamHI and KpnI, gel purified and ligated to the respective genes, as described above. The construct pMaxVax-CD28BP (see Figure 22A), which includes the nucleotide sequence encoding a CD28BP (here, e.g., SEQ ID NO:19), can be used for in vivo and in vitro expression in human and other mammalian cells and other cells in culture, including non-mammalian cells and the like.